


FORM PTO-1390 (REV 10-95)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371				MERCK 1942	
				U.S. APPLICATION NO. (If known, see 37 CFR §1.5) 09/807401	
INTERNATIONAL APPLICATION NO. PCT/EP99/07556		INTERNATIONAL FILING DATE 8 OCTOBER 1999		PRIORITY DATE CLAIMED 19 OCTOBER 1998	
TITLE OF INVENTION NATURAL FORMULATION FOR THE TREATMENT AND PREVENTION OF DEPRESSION, CONTAINING ST JOHN'S WORT AND DERIVATIVES OF DIHYDRO-AND TETRAHYDROFOLIC ACID					
APPLICANT(S) FOR DO/EO/US BUCHHOLZ, Herwig, et al.					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. §371.					
2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. §371.					
3. <input type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).					
4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19 th month from the earliest claimed priority date.					
5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. §371(c)(2))					
a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).					
b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau.					
c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).					
6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. §371(c)(2)).					
7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))					
a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).					
b. <input type="checkbox"/> have been transmitted by the International Bureau.					
c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.					
d. <input checked="" type="checkbox"/> have not been made and will not be made.					
8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).					
9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).					
10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).					
Items 11. to 16. below concern document(s) or information included:					
11. <input type="checkbox"/> An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.					
12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.					
13. <input checked="" type="checkbox"/> A FIRST preliminary amendment.					
<input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.					
14. <input type="checkbox"/> A substitute specification.					
15. <input type="checkbox"/> A change of power of attorney and/or address letter.					
16. <input type="checkbox"/> Other items or information:					

U.S. APPLICATION NO. (if known) 097/807401 <small>(37 CFR §1.5)</small>		INTERNATIONAL APPLICATION NO. PCT/EP99/07556		ATTORNEY'S DOCKET NUMBER MERCK 1942	
17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)): Search Report has been prepared by the EPO or JPO..... \$860.00 International preliminary examination fee paid to USPTO (37 CFR §1.482)..... \$690.00 No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... \$710.00 Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... \$1000.00 International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... \$100.00 <div style="text-align: right; margin-top: 10px;">ENTER APPROPRIATE BASIC FEE AMOUNT =</div>				CALCULATIONS PTO USE ONLY <div style="border: 1px solid black; height: 150px; width: 100%;"></div>	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 C.F.R. §1.492(e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30					
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	x \$ 18.00	\$0.00	
Independent claims	1 - 3 =	0	x \$ 80.00	\$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$ 270.00		
TOTAL OF ABOVE CALCULATIONS =				\$860.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).					
SUBTOTAL =				\$860.00	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 C.F.R. §1.492(f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30					
TOTAL NATIONAL FEE =				\$860.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). \$40.00 per property.					
TOTAL FEES ENCLOSED =				\$860.00	
				Amount to be refunded:	
				charged:	
a. <input checked="" type="checkbox"/> A check in the amount of <u>\$860.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>13-3402</u> in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-3402</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Customer Number 23,599 <div style="display: flex; justify-content: space-between; align-items: flex-end; margin-top: 20px;"> <div style="text-align: center;">  23599 <small>PATENT TRADEMARK OFFICE</small> </div> <div style="text-align: right;"> <div style="border-bottom: 1px solid black; width: 150px; margin-bottom: 5px;"></div> SIGNATURE <div style="border-bottom: 1px solid black; width: 150px; margin-bottom: 5px;"></div> Anthony J. Zelano NAME <div style="border-bottom: 1px solid black; width: 150px; margin-bottom: 5px;"></div> 27,969 REGISTRATION NUMBER </div> </div> <div style="margin-top: 10px;"> Filed: 13 APRIL 2001 AJZ:kms </div>					

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No. : PCT/EP99/07556
International Filing Date : 8 OCTOBER 1999
Priority Date(s) Claimed : 19 OCTOBER 1998
Applicant(s) (DO/EO/US) : BUCCHOLZ, Herwig, et al.

Title: NATURAL FORMULATION FOR THE TREATMENT AND PREVENTION OF
DEPRESSION, CONTAINING ST JOHN'S WORT AND DERIVATIVES OF
DIHYDRO- AND TETRAHYDROFOLIC ACID

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of
the above-identified International application, please amend as follows:

IN THE SPECIFICATION:

Page 1, before paragraph 1, please insert the following new paragraph:

--This application claims the benefit of priority from U.S. Provisional Application
60/104,710, filed October 19, 1998.--

IN THE CLAIMS:

3. (Amended) Formulation according to claim 1 comprising a derivative of folic acid
selected from the group consisting of 5-methyltetrahydrofolic acid, tetrahydrofolic acid,
dihydrofolic acid, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5, 10-
methylenetetrahydrofolic acid and 5-methenyltetrahydrofolic acid or their suitable salts.

5. (Amended) Formulation according to claim 1 in the form of a dosage unit,
comprising 400 to 5000 mcg of dihydro- or tetrahydrofolic acid derivatives.

[illegible]

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Respectfully submitted,

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicants
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard, Suite 1400
Arlington, VA 22201
Direct Dial: 703-812-5311
Facsimile: 703-243-6410
Email: zelano@mwzb.com

AJZ:jmm

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

A new first paragraph was inserted on page 1 of the specification. No marked up version is necessary.

In the Claims:

Claims 3, 4 and 6 have been amended as follows:

3. (Amended) Formulation according to ~~claims~~claim 1 ~~or 2~~ comprising a derivative of folic acid selected from the group consisting of 5-methyltetrahydrofolic acid, tetrahydrofolic acid, dihydrofolic acid, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5, 10-methylenetetrahydrofolic acid and 5-methenyltetrahydrofolic acid or their suitable salts.

5. (Amended) Formulation according to ~~claims~~claim 1 ~~to 4~~ in the form of a dosage unit, comprising 400 to 5000 mcg of dihydro- or tetrahydrofolic acid derivatives.

6. (Amended) Formulation according to ~~claims~~claim 1 ~~to 4~~ in the form of a dosage unit, comprising 400 to 5000 mcg of 5-formyltetrahydrofolic acid or its salts, 50 mg to 2000 mg of betaine anhydrous and 0.5 to 10 mcg of vitamin B12.

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09/807401

NATURAL FORMULATION FOR THE TREATMENT AND PREVENTION OF DEPRESSION, CONTAINING ST JOHN'S WORT AND DERIVATIVES OF DIHYDRO- AND TETRAHYDROFOLIC ACID

5 The present invention relates to novel compositions containing a combination of the plant St. John's Wort (*Hypericum perforatum* L.) and derivatives of folic acid. This natural formulation is useful for the treatment and prevention of depression with a better effect than the ingredient compounds alone.

10 Depression is an increasingly common psychiatric disorder, affecting a large part of the population, especially in developed countries. The etiology and precise mechanisms of depressive disorders are not completely understood, but are believed to involve the decrease of certain neurotransmitters, particularly serotonin (5-HT) and its metabolite, 5-hydroxyindole acetic acid (5-HIAA) in the central nervous system. High level of homocysteine and both folate and vitamin B12 deficiency are also linked to the etiology of depression.

15 Modern standard pharmacological antidepressant agents can be divided into several major groups: selective serotonin reuptake inhibitors, tricyclic and other heterocyclic antidepressants, monoamine oxidase (MAO) inhibitors, etc. 20 All of them provoke a wide range of adverse effects - from undesirable psychostimulation to hypertension and cardiotoxicity.

25 Despite some progress in this area and the availability of new antidepressants with fewer side effects, this direction of research has not granted a safe and efficient way to treat depression.

Therefore, there is a need for an innovative formulation based on the natural metabolites useful for the prevention and treatment of depression.

30 Now it has been found that the combination of natural compounds - St. John's Wort or its extracts or active ingredients and folic acid derivatives - constitutes a unique safe multifaceted approach to the prevention and treatment of mild to moderate forms of depression.

35 St. John's Wort is a perennial flowering plant that has been traditionally used in folk medicine for thousands of years due to its anti-inflammatory, analgesic and sedative properties, particularly for wound healing and treatment of respiratory infections (see Miller, A.L., 1998, Altern. Med. Rev. 3,1,18-26).

Recently it attracted attention as an effective agent for the treatment of mild to moderate depression and also of the seasonal affective disorder. Other indications include psychovegetative dysfunctions, anxiety, nervous restlessness and similar disorders. About 30 clinical studies confirmed that the efficacy of St. John's Wort (SJW) is compared to popular synthetic antidepressants (amitriptyline, imipramine, maprotiline, etc.) without any side effects (see Lieberman, S., 1998, *Altern. Complement. Therapies*, June, 163-168). It did not lead to the impairment of attention, concentration or reaction. The only side effect mentioned in the literature is the reversible increased photosensitivity to UV light after prolonged use of the St. John's Wort extract (see Golsch, S. et al., 1997, *Hautarzt* 48, 4, 249-252). No negative drug interaction associated with St. John's Wort is reported.

The mechanism of action of SJW is not completely defined. In its extract there could be identified eight secondary metabolites so far: amentoflavone, biapigenin, hyperforin, hypericin, hyperosid, pseudohypericin, quercetin and rutin (see Buter, B. et al., 1998, *Planta Med.* 64, 5, 431-437).

There are indications that hypericin, one active compound from SJW is a strong inhibitor of catechol-O-methyltransferase (see Mueller, W.E.G. et al., 1994, *J. Geriatr. Psychiatr. Neurol.* 7(Suppl. 1), 63-64; Mueller, W.E.G., 1995, *Wissenschaftlicher Bericht*, Lichtwer Pharma GmbH, Berlin) and monoamine oxidases (see Suzuki, O. et al., 1984, *Planta Med.* 50, 272-274). Monoamine oxidases participate in the breakdown of neurotransmitters serotonin and noradrenalin (see Perovic, S. et al., 1995, *Arzn. Forsch/Drug Res.* 45, 1145-1148).

Further effects include the modulation of the serotonin receptors or/and a general influence of hypericum extracts on central dopaminergic neurons (see Butterweck, V. et al., 1998, *Planta Med.* 64, 4, 291-294).

Other reports suggest that since pure hypericin shows no inhibiting effect on MAO (see Bladt, S. et al., 1994, *J. Geriatr. Psychiatr. Neurol.* 7, Suppl. 1, 57-59), the antidepressive effect of SJW cannot be explained in terms of MAO inhibition. In a series of recent publications it has been demonstrated that hyperforin, a major lipophilic non-nitrogenous constituent of SJW (and of *Hyperici Oleum*), is also a potent inhibitor of uptake of serotonin, dopamine,

noradrenaline, GABA, and L-glutamate in vitro (see Chattarjee, S.S. et al., 1998, Life Sci. 63, 6, 499-510).

Most of the known pharmacological properties of the SJW extract can also be demonstrated with pure hyperforin. Therefore it has been suggested that hyperforin could be a major active principle of the plant (see Laakmann, G. et al., 1998, Pharmacopsychiatry 31, Suppl. 1, 54-59). Most researchers agree that the combination of low-grade monoamino oxidase inhibition and noradrenaline and serotonin re-uptake blockade seems to be the most likely mechanism of action of SJW (see Nordfors, M. et al., 1997, Lakartidningen 94, 25, 2365-2367).

A close relationship between folate metabolism and depression is well documented (see Alpert, J.E. et al., 1997, Nutrition Reviews 55, 5, 145-149). It is known that depressive symptoms are the most common indicator of folate deficiency. Depressed patients have been consistently found to have lower serum folate concentrations than control subjects (see Fava, M. et al., 1997, Am. J. Psychiatry 154, 426-428). Recently, low folate levels were linked to the poor response to selective serotonin uptake inhibitors.

The biochemical mechanisms by which folic acid derivatives affect the neuropsychiatric status apparently involve transmethylation reactions with components (DNA, RNA, proteins, biomembranes) of the central nervous system. The methyl group from folate (in the form of active metabolite 5-methyltetrahydrofolic acid, 5-MTHF, or 5-formyltetrahydrofolic acid, after being reduced to 5-MTHF) is transferred to homocysteine to form methionine. The de novo synthesis of methionine requires vitamin B12, since it involves a reaction catalyzed by vitamin B12-dependent methionine synthetase. Methionine then participates in the reaction producing S-adenosylmethionine which is an important intermediate in more than 35 transmethylation reactions in CNS (see Bottiglieri, T. et al., 1994, Drugs 48, 137-152). Among reactions relevant to the effect of folate level on depression is the synthesis of tetrahydrobiopterin, a cofactor in the hydroxylation of phenylalanine and tryptophan playing a crucial role in the biosynthesis of the neurotransmitters dopamine, norepinephrine and serotonin.

5 The significant beneficial impact of the suggested composition on psychoneurological status is expected through a reduction of high levels of homocysteine in the brain due to 5-methyl-tetrahydrofolic acid treatment. High levels of homocysteine have been recognized as a major risk factor for a wide range of diseases including neurological and cerebrovascular diseases. In particular, increased plasma homocysteine level has been linked to depression, mental and severe psychomotoric retardation.

10 Among major causes of hyperhomocysteinemia are genetic deficiencies of methylenetetrahydrofolate reductase (MTHFR) or cystathionine β -synthase (CS), key enzymes in the metabolism of folic acid. Methylenetetrahydrofolate reductase deficiency is a relatively common disorder, and about 15 % of the general population have abnormal MTHFR genotype. A successful treatment of hyperhomocysteinemia with folic acid and cofactors of folic acid metabolism (e.g. vitamin B6 and vitamin B12) has been documented in numerous studies (see Bottiglieri, T., 1996, Nutrition Reviews 54, 12, 382-390).

15 The active metabolite in the folic acid pathway is 5-methyltetrahydrofolic acid which, orally administered, should be more efficacious than folic acid. Folic acid given to the patients has to go through several reactions including a MTHFR catalyzed reaction to produce 5-methyltetrahydrofolic acid. All these steps can be by-passed with the direct introduction of 5-methyltetrahydrofolic acid. Of major importance is that 5-methyltetrahydrofolic acid is the only metabolite which is able to pass the blood-brain barrier. However, because of the possible conversion of other folic acid derivatives to 5-methyltetrahydrofolic acid, it is certainly possible to use for example 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5,10-methylenetetrahydrofolic acid, 5-methenyltetrahydrofolic acid, tetrahydrofolic acid, dihydrofolic acid and folic acid itself.

25
30 Surprisingly it has been found that St. John's Wort, a traditional soft antidepressant which improves the psychovegetative conditions by modulating the action of neurotransmitters, and 5-methyltetrahydrofolic acid which improves the psychiatric condition by a reduction of the homocysteine concentration in the brain augment their beneficial effect when used in combination. As the results of their synergistic effect, symptoms of depression are removed and

35

also metabolic conditions of the central nervous system are improved. This leads to a decrease of intensity and frequency of attacks of depression.

Therefore, the object of the present invention is an orally applicable natural formulation comprising St. John's Wort (*Hypericum perforatum*) or its extracts or active ingredients in combination with folic acid derivatives or suitable salts thereof.

These natural formulations are highly useful for the prevention and the therapy of depression.

The St. John's Wort may be used as the whole plant, its water extract, ethanol or any other extract. It is also possible to use just one or more of the plants ingredients. Especially preferred is the hypericin which is commercially available in different concentrations (e.g. 0.3% Hypericin St. John's Wort, Fa. Lichtwer, Berlin).

As the second ingredient folic acid derivatives selected from the group consisting of 5-methyltetrahydrofolic acid, tetrahydrofolic acid, dihydrofolic acid, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5,10-methylentetrahydrofolic acid and 5-methenyltetrahydrofolic acid or their suitable salts are used.

5-methyltetrahydrofolic acid or 5-formyltetrahydrofolic acid are especially preferred.

The folic acid derivatives may also be in the form of their salts. Preferred are suitable salts like their sodium or calcium salts.

In the case of application of 5-formyltetrahydrofolic acid, additional ingredients should be vitamin B12 and betaine anhydrous. Betaine is a donor for methyl groups which are transferred by vitamin B12 to homocysteine.

Useful compositions may contain in one serving 400 to 5 000 mcg of folic acid derivative and in case of 5-formyltetrahydrofolic acid 50 mg to 1 000 mg betaine and 0,5 to 10 mcg vitamin B12. The dose of St. John's Wort can be adjusted to the particular case in a wide range. Preferably a commercially available extract of 0.3 % Hypericin is applied in an amount of 100 mg to 1000 mg.

The formulations according to the present invention may be prepared in form of tablets, gelcaps, capsules or syrups.

The compositions of the present invention preferably are useful as food supplements, but they may also be administered in a pharmaceutical treatment.

The present invention makes available:

- a) a method of prevention of neurological and psychopathological diseases;
- b) a method of supporting a pharmacological treatment of neurological and psychopathological diseases;
- c) a method leading to a decrease of intensity and frequency of attacks of depression;
- d) a natural approach without any side effects for the prevention and treatment of depression;

by oral administration of a formulation described above and/or related and suggested above modifications of this composition.

Thus, this invention provides an innovative formulation based on natural ingredients useful for the prevention and treatment of depression. The combination of the natural compounds - St. John's Wort or its extracts or active ingredients and derivatives of dihydro- and tetrahydrofolic acid, derivatives thereof or corresponding salts - constitutes a unique and safe approach to the prevention and treatment of mild to moderate forms of depression without any side effects.

The entire disclosure of all applications, patents and publications, cited above and below are hereby incorporated by reference.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

Examples

Example 1

5 A lower dosed formulation according to the invention is obtained by mixing the following components:

300 mg of 0.3 % Hypericin St. John's Wort (Fa. Lichtwer, Berlin) and
400 mcg of 5-methyltetrahydrofolic acid calcium salt,
formulated in gelcaps.

10 Example 2

A higher dosed formulation is obtained by mixing
600 mg of 0.3 % Hypericin St. John's Wort and
800 mcg of 5-methyltetrahydrofolic acid calcium salt,
15 formulated in gelcaps.

Example 3

A formulation according to the invention is obtained by mixing
300 mg of 0,3 % Hypericin St. John's Wort,
20 400 mcg of 5-formyltetrahydrofolic acid calcium salt,
300 mg betaine anhydrous and
3 mcg vitamin B12 (cyanocobalamin),
formulated in gelcaps.

25 Example 4

A higher dosed formulation is obtained by mixing
600 mg of 0,3 % Hypericin St. John's Wort,
800 mcg of 5-formyltetrahydrofolic acid calcium salt,

30 600 mg betaine anhydrous and
6 mcg vitamin B12 (cyanocobalamin),

formulated in gelcaps.

Claims

1. Orally applicable natural formulation comprising St. John's Wort (*Hypericum perforatum*) or its extracts or active ingredients in combination with derivatives of dihydro- and tetrahydrofolic acid or suitable salts thereof.
2. Formulation according to claim 1 comprising Hypericin St. John's Wort in form of its water or alcohol extract.
3. Formulation according to claim 1 or 2 comprising a derivative of folic acid selected from the group consisting of 5-methyltetrahydrofolic acid, tetrahydrofolic acid, dihydrofolic acid, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5,10-methylenetetrahydrofolic acid and 5-methenyltetrahydrofolic acid or their suitable salts.
4. Formulation according to claim 3 comprising 5-formyltetrahydrofolic acid or its salts which comprises additionally vitamin B12 and betaine anhydrous.
5. Formulation according to claims 1 to 4 in the form of a dosage unit, comprising 400 to 5000 mcg of dihydro- or tetrahydrofolic acid derivatives.
6. Formulation according to claims 1 to 4 in the form of a dosage unit, comprising 400 to 5000 mcg of 5-formyltetrahydrofolic acid or its salts, 50 mg to 2000 mg of betaine anhydrous and 0,5 to 10 mcg of vitamin B12.
7. A method of using the formulation according to claim 1 which comprises employing the formulation of claim 1 as a food supplement.
8. Method of prevention of neurological and psychopathological diseases which comprises orally administering a formulation according to claim 1.
9. Method of supporting a pharmacological treatment of neurological and psychopathological diseases which comprises orally administering a formulation according to claim 1.

INVENTOR INFORMATION

Inventor One Given Name::	Herwig
Family Name::	BUCHHOLZ
Mailing Address Line One::	Auf dem Muhlberg 75
City::	Frankfurt
Country::	Germany
Postal or Zip Code::	D-60599
Citizenship Country::	Germany
Inventor Two Given Name::	Angela
Family Name::	DUDDA
Mailing Address Line One::	Kaiser-Sigmund-Strasse 32
City::	Frankfurt
Country::	Germany
Postal or Zip Code::	D-60320
Country of Residence::	Germany
Citizenship Country::	Germany
Inventor Three Given Name::	Jerzy
Family Name::	MEDUSKI
Mailing Address Line One::	6806 Vista Del Mar Lane
City::	Playa Del Rey
State or Province::	California
Country::	US
Postal or Zip Code::	90298-7640
Country of Residence::	US
Citizenship Country::	US

CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 23599

APPLICATION INFORMATION

Title Line One::	NATURAL FORMULATION FOR THE TREATMENT
Title Line Two::	AND PREVENTION OF DEPRESSION,
Title Line Three::	CONTAINING ST JOHN'S WORT AND
Title Line Four::	DERIVATIVES OF DIHYDRO-AND
Title Line Five::	TETRAHYDROFOLIC ACID
Application Type::	UTILITY
Docket Number::	MERCK 1942

REPRESENTATIVE INFORMATION

Representative Customer Number:: 23599

PRIOR FOREIGN APPLICATIONS

Foreign Application One::	PCT/EP99/07556
Filing Date::	10/8/99
Country::	PCT
Priority Claimed::	YES
Foreign Application Two::	60/104,710

Filing Date:: 10/19/98
Country:: US
Priority Claimed:: YES

ASSIGNEE INFORMATION

Name of Assignee:: MERCK PATENT GMBH
Address Line One:: Frankfurter Strasse 250
City:: Darmstadt
Country:: Germany
Postal or Zip Code:: D-64293

Docket No. Merck

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Natural formulation for the treatment and prevention of depression, containing St John's wort and derivatives of dihydro- and tetrahydrofolic acid

the specification of which

(check one)

- ☐ is attached hereto.
- ☒ was filed on 08.10.1999 as United States Application No. or PCT International Application Number PCT/EP99/07556 and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

<u>60/104,710</u> (Number)	<u>USA</u> (Country)	<u>19.10.1998</u> (Day/Month/Year Filed)	<input type="checkbox"/>
<u> </u> (Number)	<u> </u> (Country)	<u> </u> (Day/Month/Year Filed)	<input type="checkbox"/>
<u> </u> (Number)	<u> </u> (Country)	<u> </u> (Day/Month/Year Filed)	<input type="checkbox"/>

T 0 8 1 1 0 " T 0 4 2 0 2 5 0

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

I. William Millen (Reg. No. 19,544)
 John L. White (Reg. No. 17,746)
 Anthony J. Zelano (Reg. No. 27,969)
 Alan E.J. Branigan (Reg. No. 20,565)
 John R. Moses (Reg. No. 24,983)
 Harry B. Shubin (Reg. No. 32,004)
 Brion P. Heaney (Reg. No. 32,542)
 Richard J. Traverso (Reg. No. 30,595)

Diana Hamlet-King (Reg. No. 33,302)
 John A. Sopp (Reg. No. 33,103)
 Richard E. Kurtz (Reg. No. 33,936)
 Richard M. Lebovitz (Reg. No. 37,067)
 John H. Thomas (Reg. No. 33,460)
 Luan Cao Do (Reg. No. 38,434)

Send Correspondence to: MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Blvd., Suite 1400
Arlington, VA 22201

Direct Telephone Calls to: (name and telephone number)
Harry B. Shubin (703) 812-5306

Full name of sole or first inventor	
<u>Herwig BUCHHOLZ</u>	
Sole or first inventor's signature	Date
<u>[Signature]</u>	<u>February 19, 2001</u>
Residence	
<u>60599 Frankfurt, Germany</u>	
Citizenship	
<u>German</u>	
Post Office Address	
<u>c/o MERCK KGaA</u>	
<u>64271 Darmstadt, Germany</u>	

Full name of second inventor, if any	
<u>Angela DUDDA</u>	
Second inventor's signature	Date
<u>[Signature]</u>	<u>February 19, 2001</u>
Residence	
<u>60320 Frankfurt, Germany</u>	
Citizenship	
<u>German</u>	
Post Office Address	
<u>c/o MERCK KGaA</u>	
<u>64271 Darmstadt Germany</u>	

Full name of third inventor, if any

Jerzy MEDUSKI

Third inventor's signature

February 19, 2001 Date

Residence

CA 90298-7640, USA CA

Citizenship

US

Post Office Address

c/o Merck KGaA

64271 Darmstadt, Germany

Full name of fourth inventor, if any

Fourth inventor's signature

Date

Residence

Citizenship

Post Office Address

Full name of fifth inventor, if any

Fifth inventor's signature

Date

Residence

Citizenship

Post Office Address

Full name of sixth inventor, if any

Sixth inventor's signature

Date

Residence

Citizenship

Post Office Address